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MOBAY CORP

Contractor

CHEMAGRO DIV OF BAYCHEM CORP

Document Title

ACUTE TOXICITY STUDIES OF CYCLOHEXYL ISOCYANATE WITH COVER LETTER DATED 121090

Chemical Category

CYCLOHEXYL ISOCYANATE (3173-53-3)

CONTAINS NO CBI **Mobay**

A Bayer USA INC COMPANY

Mobay Corporation
Health, Environment, Safety
& Plant Management

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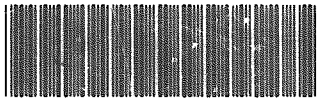

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Office of Toxic Substances Room L-100
Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Attention: 8(d) Health and Safety Reporting Rule
(Notification/Reporting)

Gentlemen:

Enclosed is a copy of Health and Safety Studies, submitted on behalf of Mobay Corporation, Mobay Road, Pittsburgh, Pennsylvania 15205. We are filing these Health and Safety Studies to comply with the regulations codified at 40 CFR, Part 716.

The information required at 40 CFR 716.35 is given below.

Chemical Name: Cyclohexane, isocyanato-

CAS No: 3173-53-3

Name of Study: Acute Toxicities of Cyclohexyl isocyanate

Submitting Official: Francis J. Rattay
Title: Manager, Regulatory Compliance
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Sincerely,

Francis J. Rattay

Francis J. Rattay
Manager, Regulatory Compliance

Attachment
cc: J. R. Bankston
8(d) File

Certified Mail No.: P 520 613 276

Report No. 40870

CHEMAGRO Division of Baychem Corporation
Research and Development

TITLE: Acute Toxicity Studies of Cyclohexyl Isocyanate

AUTHORS: C. R. Crawford and R. H. Anderson

ABSTRACT: Some acute toxicity studies have determined that cyclohexyl isocyanate is a very toxic compound and causes extreme eye irritation.

REFERENCE: 68-22, 73-123

DATE: June 14, 1974

APPROVED BY: L. Sheila-L. Nelson
D. L. Nelson

Cyclohexyl
Isoc
E-203

Report No. 40870

Title:

Acute Toxicity Studies of Cyclohexyl Isocyanate

Introduction:

Laboratory personnel and scientists are exposed to many chemical compounds whose toxicological risks are not known. These risks must be evaluated as soon as possible so that the potential health hazard associated with the handling of the compound can be determined. The purpose of this study is to characterize the potential hazard associated with the use of cyclohexyl isocyanate.

Experimental:

Male Sprague-Dawley rats weighing 270-300 g and females weighing 200-250 g were used in the oral studies. The animals were fasted 20-24 hours before the compound was administered. The compound was diluted with a 20% ethanol-80% propylene glycol solution to give a final concentration so that each animal received its dose in a volume equivalent to 0.1-0.2% body weight. Graded doses of the compound were given to 4 groups of rats with a slightly curved stainless steel 3 inch animal feeding needle. Each group consisted of 4 animals. Symptoms and mortality were recorded for 14 days, and the LD_{50} was calculated by the method of Weil (Carrol S. Weil, Biometrics, 8, 349, 1952). In the dermal toxicity studies New Zealand white rabbits weighing 2-3 kg were used. Cyclohexyl isocyanate was applied undiluted to the shaved backs of the animals and was in contact with the bare skin for 24 hours. The animals were placed in animal restraining boxes for 24 hours after which the compound was removed. Symptoms and mortality were recorded for 14 days.

A proposed revision of 21 CFR, Paragraph 191.11 for determining the skin irritancy of substances as recommended by the Food and Drug Administration and a proposed procedure [Revision of Paragraph 191.12 of the Hazardous Substances Regulation (21 CFR 191.12)] for determining eye irritancy of substance were used in this study.

Mature New Zealand white rabbits were used throughout the irritant studies. The animals were prepared dermally by closely shaving a large area of their backs with electric clippers equipped with a No. 40 head on the day the test substance was applied. The eyes of the animals were examined one day prior to the instillation of the test substance to exclude those animals with obvious eye defects.

For the dermal study the compounds were applied to 2 areas of the shaved backs of the animals. One area was abraded by scrubbing it briskly with a nail brush. The other area was left intact. A quantity of material equivalent to 500 mg was applied to each area. In those cases where this quantity would be lethal, lesser amounts were used. These areas were covered with a one inch square gauze patch and the patch was subsequently

covered with a 2 inch x 2 inch piece of rubber to prevent shifting of solid substances and to retard evaporation of highly volatile compounds. The trunks of the animals were loosely wrapped in aluminum foil. The animals were restrained for 4 hours after which the bandage and compounds were removed. At this time and at 24 and 48 hours the treated areas were examined. Scoring of the reaction was based on the amount of redness, edema and necrosis found. To be classed as a dermal irritant a substance must have an average irritation score of 5 or more.

The eye irritancy of the compounds was studied by instilling a quantity of substance equivalent to 100 mg in the left eye of the animals. The right eye served as a control. The substance was instilled by pulling the lower lid away from the eye to form a cup into which the substance was placed.

The lid was raised to close with the upper one and the 2 lids were held firmly together for a few seconds before the animal was released. The eyes were examined for conjunctival redness, conjunctival chemosis, corneal and iridal opacity and iridal, corneal and conjunctival ulcerations using as a reference the "Illustrated Guide for Grading Eye Irritation by Hazardous Substance" published by the U. S. Department of Health, Education and Welfare, Food and Drug Administration. The eyes were examined for corneal ulceration by instilling one drop of 2% fluorescein sodium ophthalmic solution in the treated eye 1, 3 and 7 days after instillation and subsequent periods if needed. The eye was flushed immediately with saline at room temperature and examined under ultraviolet light for corneal ulceration.

The animals were exposed to the test substance for 5 minutes after which the eyes were washed for 2 minutes with 300 ml water. The animals were examined 1, 24, 48 and 72 hours and 7 days after washing. Further examination of the eyes at 14 and 21 days depended on the condition of the eye at 7 days. If ulceration or opacity was shown at 7 days the eyes were examined at 14 days and at 21 days if ulceration or opacity was shown at 14 days.

Vapor Inhalation - Description of Apparatus

The chamber for determining vapor toxicity was rectangular and of a slight tapering plastic design. The dimensions were 12 x 10.75 x 9.87 inches. The walls of the chamber were 1/8 inch thick. The lid contained a thermometer and a 3/8 inch metal outlet pipe. The lid was gasketed with rubber tubing. An inlet 3/8 inch metal pipe was situated in one wall approximately 2 inches above the floor of the chamber. Animals were supported on 2 removable wire mesh racks. To view the animals during exposure, a 5 1/2 x 6 1/2 glass window was installed in one wall of the chamber. The capacity of the chamber was approximately 20 liters. The vapors were generated from a known quantity of test solution by passing a stream of air through the solution contained in a flask. The flow was then passed to a one liter trap to remove droplets and then to the chamber. The intake air was supplied from laboratory compressed air line modified so that the pressure was sufficient to agitate the solution. The flow of air was measured by a calibrated flowmeter.

Results:

The acute oral toxicity of cyclohexyl isocyanate is summarized in Table 1. Rats exhibited symptoms of lethargy which was of rapid onset and, depending on dose, proceeded to profound sedation. Approximately 16 hours after dosing there was evidence of weeping bloody tears and generalized tremors were exhibited on provocation. When rabbits were exposed dermally the only obvious symptom was tachypnea. Exposure of rats to vapors of the compound caused a noticeable eye irritation, dyspnea, salivation, piloerection and death to all animals exposed. The compound causes eye irritation (Table 2), but not dermal irritation (Table 3) to rabbits.

Conclusion:

Cyclohexyl isocyanate is a very toxic compound. Particular care should be exercised in handling the material.

Table 1. Acute Oral, Dermal and Vapor Toxicity of Cyclohexyl Isocyanate

Report No. _____

Compound	Species	Sex	Route of Exposure	Dose mg/kg	Chamber Concentration	Observations Deaths/ Symptoms/No. Exposed	Symptoms Start (Min)	Symptoms End (Day)	Time of Death (Hours)	LD_{50} (95% Confidence Limits) (mg/kg)
Cyclohexyl Isocyanate (Technical)	Rat	Male	Oral	100	-	0/4/4	240	1	-	
				200		1/4/4	120	1	24	
				400		2/4/4	60	2	18	
				800		4/4/4	45	-	18-48	335 (198 to 569)
Cyclohexyl Isocyanate (Technical)	Rat	Female	Oral	400	-	0/4/4	180	1	-	
				500		1/4/4	90	1	5	
				625		1/4/4	60	1	18	
				781		4/4/4	30	-	3-24	625 (533 to 731)
Cyclohexyl Isocyanate (Technical)	Rabbit	Male	Dermal	200	-	0/0/1	-	-	-	
		Female	Dermal	500		1/1/1	15	-	25	
		Female	Dermal	1000		1/1/1	15	-	5	
		Male	Dermal	2000		1/1/1	15	-	2	MLD = 500 mg/kg
Cyclohexyl Isocyanate (Technical)	Rat	Male	Inhalation	-	Air saturated with vapors of product.	4/4/4	23	-	2	-
Cyclohexyl Isocyanate (Technical)	Rat	Female	Inhalation	-	Air saturated with vapors of product.	4/4/4	23	-	2	-

Report No._____

Table 2. Eye Irritancy of Cyclohexyl Isocyanate

Rabbit	Quantity Placed in Eye (ml)	Exposure Time (Min)		Observations: 1 Hour After Wash	24 Hours	48 Hours	72 Hours	7 Days	14 Days	21 Days
4	0.1	5	Cornea							
			Ulceration	0	4	-	4	4	4	4
			Opacity	2	2	3	4	4	4	3
			Iris	0	0	0	0	0	0	0
			Conjunctiva							
			Erythema	1	1	2	2	3	1	0
			Chemosis	3	4	4	4	4	2	0
			Ulceration	4	4	-	4	0	0	0
6	0.1	5	Cornea							
			Ulceration	0	4	-	4	4	4	4
			Opacity	2	2	3	4	3	3	2
			Iris	0	0	0	0	0	0	0
			Conjunctiva							
			Erythema	1	2	2	3	2	0	0
			Chemosis	3	4	4	4	4	2	0
			Ulceration	4	4	-	4	0	0	0

Table 3. Dermal Irritation of Cyclohexyl Cyanate

Report No. _____

Rabbit	Quantity Placed on Skin Area (ml)	Observation						Primary Irritation Score
		Abraded			Unabraded			
		4 Hour	24 Hour	48 Hour	4 Hour	24 Hour	48 Hour	
41	0.1	Redness - 1 Edema - 4	Redness - 1 Edema - 2	Redness - 1 Edema - 0	Redness - 1 Edema - 4	Redness - 1 Edema - 2	Redness - 1 Edema - 0	3.00
28	0.1	Redness - 2 Edema - 3	Redness - 0 Edema - 0	Redness - 0 Edema - 0	Redness - 2 Edema - 3	Redness - 0 Edema - 0	Redness - 0 Edema - 0	1.67
							Average Irritation Score	2.33